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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/039,761	10/19/2001	Brian Wong	A-70224/RMS/TAL/DHR	9200

20350 7590 06/11/2004

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EXAMINER	
MURPHY, JOSEPH F	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 06/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/039,761	WONG ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *6-10, 16-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 11-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/25/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Comparison A*.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-5, 11-15 in the paper of 3/29/2004 is acknowledged. The traversal is on the ground(s) that the four Groups set forth tin the restriction requirement all stem from a common concept and theory, and that searching all the Groups would not result in a burden on the Examiner. This is not found persuasive because Groups I and II make use of different nucleic acids encoding different proteins, while Groups III and IV are distinct because they make use of different proteins with distinct structures. Groups I-II and III-IV are distinct because they require different starting materials and steps. Thus the Groups are independent and distinct, and a burden would be imposed on the Examiner to search all Groups.

The requirement is still deemed proper and is therefore made FINAL. Claims 6-10, 16-27 are withdrawn from consideration pursuant to 37 CFR 1.142(b).

Claim Objections

Claims 1-5, 11-15 are objected to because of the following informalities: According to 37 CFR 1.821(d) (MPEP § 2422), where the description or claims of a patent application discuss a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application. Sequences are referred to in claims 1 and 11 as appearing in Figure 1 or 2 but are not identified by SEQ ID NO as required.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 11, 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, which is enabling for methods of identification of agents capable of modulating the activity of a protein 95% identical to the USP-25 protein, with the sequence as set forth in SEQ ID NO: 2, wherein the assay uses a target protein fused with ubiquitin and further wherein the target protein is UBC9, SYK or calcineurin, and further wherein the ubiquitin like protein is SMT3/SUMO, NEDD8/RUBY, does not reasonably provide enablement for methods of identification of agents capable of modulating the activity of a protein 95% identical to the USP-25 protein, with the sequence as set forth in SEQ ID NO: 2, wherein the assay uses a target protein fused with ubiquitin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to for methods of identification of agents capable of modulating the activity of a protein 95% identical to the USP-25 protein, with the sequence as set forth in SEQ ID NO: 2, wherein the assay uses a target protein fused with ubiquitin. Claims 1, 5, 11, 15 are overly broad since insufficient guidance is provided as to which protein will serve as a target for USP-25. The claims are directed to methods using variant polypeptides, while the Specification only teaches the use of target proteins comprising UBC9, SYK or calcineurin, and wherein the ubiquitin like protein is SMT3/SUMO, NEDD8/RUBY. Since the claims encompass variant

polypeptides and given the unpredictability of the effect of variations on protein function, it would require undue experimentation to practice the claimed invention. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The amino acid sequence of a polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the target polypeptide are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicant is required to enable one of skill in the art to practice the claimed invention, while the claims encompass target polypeptides which the specification only teaches one skilled in the art to test for functional variants. It would require undue experimentation for one of skill in the art to practice the claimed invention.

Claims 1, 5, 11, 15 are rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to for methods of identification of agents capable of modulating the activity of a protein 95% identical to the USP-25 protein, with the sequence as set forth in SEQ ID NO: 2, wherein the assay uses a target protein fused with ubiquitin. These are genus claims because the claims are thus directed to methods using variant polypeptides. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the use of target proteins comprising UBC9, SYK or calcineurin, and the ubiquitin like proteins SMT3/SUMO, NEDD8/RUBY is insufficient to describe the genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides. There is no description of the conserved regions that are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide

compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the target polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1-5, 11-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 11 are vague and indefinite in the recitation of the term "protein activity". The term " protein activity " is not defined by the claim, but give no definition of what this activity is. Various biological activities can be attributed to a peptide. For example, "activity" could constitute transportation throughout a cell, alteration of tertiary structure due to changes in pH, ligand binding, or modulation of second messenger effect, etc. 'Activity' could also be referring to the ability of the fragment to stimulate antibody production. Claims 2-5, 12-15 are rejected insofar as they depend on the recitation on claims 1 and 11 of "protein activity".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 0078934 (Nizetic et al.).

The claims are drawn to methods of identification of agents capable of modulating the activity of a protein 95% identical to the USP-25 protein, with the sequence as set forth in SEQ ID NO: 2, wherein the assay uses a target protein fused with ubiquitin. The claims are further drawn to methods wherein the ubiquitin like protein comprises SMT3/SUMO or NEDD8/RUBY, and wherein the target protein is, *inter alia*, UBC9. These claims are not patentable because the '934 document teaches methods using a ubiquitin specific protease, USP-25, which is 99.7%

identical to the sequence as set forth in SEQ ID NO: 2 (see Sequence comparison A, attached, and the '934 document at 27-29). The '934 document teaches methods for measuring the activity of USP-25 using a reporter gene comprising ubiquitin conjugated detectable proteins ('934 at 20). The '934 document further teaches that there is interaction between USP-25 and the ubiquitin like proteins such as SUMO-1, 2, 3 ('934 at 20). The '934 document also teaches other ubiquitin like protein such as NEDD-8 ('934 at 9). The '934 document further teaches that UBC-9 has been shown to be capable of conjugating with ubiquitin like proteins ('934 at 8). The '934 document further teaches that the USP-25 protein can interact with ubiquitin like proteins, such as Sumo-3, and UBC-9 ('934 at 20). The '934 document further teaches that ubiquitin-like molecules, fragments thereof and C-terminal modified versions thereof may be a specific inhibitor of USP-25. Therefore, it would have been obvious to one of skill in the art at the time the invention was made to practice a method of identification of agents capable of modulating the activity of a protein 95% identical to the USP-25 protein, with the sequence as set forth in SEQ ID NO: 2, wherein the assay uses a target protein fused with ubiquitin and further wherein the ubiquitin like protein comprises SMT3/SUMO or NEDD8/RUBY, and wherein the target protein is UBC9, as taught in the '934 document. The motivation is provide in the '934 document which teaches that ubiquitin analogues which compete with the ubiquitinated substrate and/or react with the protease enzyme so as to inactivate it are useful for the manufacture of a composition for treating AD.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
June 8, 2004

Sequence Comparison A

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RESULT 3
AAB31546
ID   AAB31546 standard; protein; 1055 AA.
XX
AC   AAB31546;
XX
DT   20-APR-2001  (first entry)
XX
DE   A human ubiquitin specific protease 25 (USP25).
XX
KW   Human; ubiquitin specific protease; USP; USP25; chromosome 21; q11-q21;
KW   Alzheimer's disease.
XX
OS   Homo sapiens.
XX
PN   WO200078934-A2.
XX
PD   28-DEC-2000.
XX
PF   22-JUN-2000; 2000WO-GB002423.
XX
PR   22-JUN-1999;   99GB-00014589.
PR   03-APR-2000; 2000GB-00008162.
XX
PA   (UNLO ) UNIV LONDON SCHOOL PHARMACY.
XX
PI   Nizetic D,  Groet J;
XX
DR   WPI; 2001-091566/10.
DR   N-PSDB; AAF24880, AAF24881.
XX
PT   Use of ubiquitin specific protease or ubiquitin-like specific protease
PT   for the diagnosis, treatment or prophylaxis of Alzheimer's disease.
XX
PS   Claim 7; Page 54-58; 66pp; English.
XX
CC   The present sequence represents a human ubiquitin specific protease 25
CC   (USP25). The USP gene is located on chromosome 21 long arm at q11-q21.
CC   The USP gene is implicated in Alzheimer's disease. USP25 is located in a
CC   highly methylated chromosomal region, and the CpG island that occupies
CC   the 5' regulatory sequences and 5' UTR of USP25 is differentially
CC   methylated in a tissue specific fashion. The USP polynucleotides and
CC   polypeptides, and their inhibitors are useful in the treatment,
CC   diagnosis, or prophylaxis of Alzheimer's disease, and for investigating
CC   the pathogenesis of Alzheimer's disease
XX
SQ   Sequence 1055 AA;

  Query Match             99.7%;  Score 5460;  DB 4;  Length 1055;
  Best Local Similarity   99.7%;  Pred. No. 0;
  Matches 1052;  Conservative    0;  Mismatches    3;  Indels    0;  Gaps    0;

Qy          1 MTVEQNVLQQSAAQKHQQTFLNQLREITGINDTQILQQALKDSNGNLELAVAFLTAKNAK 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MTVEQNVLQQSAAQKHQQTFLNQLREITGINDTQILQQALKDSNGNLELAVAFLTAKNAK 60

Qy         61 TPQQEETTYYQTALPGNDRYISVGSQADTNVIDLTGDDKDDLQRTIALSLAESNRAFRET 120
              |||||||||||||||||||||||||||||||||||||||||| ||||||||||||||||
Db         61 TPQQEETTYYQTALPGNDRYISVGSQADTNVIDLTGDDKDDLQRAIALSLAESNRAFRET 120

Qy        121 GITDEEQAISRVLEASIAENKACLKRTPTEVWRDSRNPYDRKRQDKAPVGLKNVGNTCWF 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 GITDEEQAISRVLEASIAENKACLKRTPTEVWRDSRNPYDRKRQDKAPVGLKNVGNTCWF 180

Qy        181 SAVIQSLFNLLEFRRLVLNYKPPSNAQDLPRNQKEHRNLPFMRELRYLFALLVGTKRKYV 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 SAVIQSLFNLLEFRRLVLNYKPPSNAQDLPRNQKEHRNLPFMRELRYLFALLVGTKRKYV 240
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Qy        241 DPSRAVEILKDAFKSNDSQQQDVSEFTHKLLDWLEDAFQMKAEEETDEEKPKNPMVELFY 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 DPSRAVEILKDAFKSNDSQQQDVSEFTHKLLDWLEDAFQMKAEEETDEEKPKNPMVELFY 300

Qy        301 GRFLAVGVLEGKKFENTEMFGQYPLQVNGFKDLHECLEAAMIEGEIESLHSENSGKSGQE 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 GRFLAVGVLEGKKFENTEMFGQYPLQVNGFKDLHECLEAAMIEGEIESLHSENSGKSGQE 360

Qy        361 HWFTGLPPVLTFXLSRFEFNQALGRPEKIHNKLEFPQVLYLDRYMHRNREITRIKREEIK 420
              |||| ||||||| ||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 HWFTELPPVLTFELSRFEFNQALGRPEKIHNKLEFPQVLYLDRYMHRNREITRIKREEIK 420

Qy        421 RLKDYLTVLQQRLERYLSYGSGPKRFPLVDVLQYALEFASSKPVCTSPVDDIDASSPPSG 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 RLKDYLTVLQQRLERYLSYGSGPKRFPLVDVLQYALEFASSKPVCTSPVDDIDASSPPSG 480

Qy        481 SIPSQTLPSTTEQQGALSSELPSTSPSSVAAISSRSVIHKPFTQSRIPPDLPMHPAPRHI 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 SIPSQTLPSTTEQQGALSSELPSTSPSSVAAISSRSVIHKPFTQSRIPPDLPMHPAPRHI 540

Qy        541 TEEELSVLESCLHRWRTEIENDTRDLQESISRIHRTIELMYSDKSMIQVPYRLHAVLVHE 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 TEEELSVLESCLHRWRTEIENDTRDLQESISRIHRTIELMYSDKSMIQVPYRLHAVLVHE 600

Qy        601 GQANAGHYWAYIFDHRESRWMKYNDIAVTKSSWEELVRDSFGGYRNASAYCLMYINDKAQ 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 GQANAGHYWAYIFDHRESRWMKYNDIAVTKSSWEELVRDSFGGYRNASAYCLMYINDKAQ 660

Qy        661 FLIQEEFNKETGQPLVGIETLPPDLRDFVEEDNQRFEKELEEWDAQLAQKALQEKLLASQ 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        661 FLIQEEFNKETGQPLVGIETLPPDLRDFVEEDNQRFEKELEEWDAQLAQKALQEKLLASQ 720

Qy        721 KLRESETSVTTAQAAGDPEYLEQPSRSDFSKHLKEETIQIITKASHEHEDKSPETVLQSA 780
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        721 KLRESETSVTTAQAAGDPEYLEQPSRSDFSKHLKEETIQIITKASHEHEDKSPETVLQSA 780

Qy        781 IKLEYARLVKLAQEDTPPETDYRLHHVVVYFIQNQAPKKIIEKTLLEQFGDRNLSFDERC 840
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        781 IKLEYARLVKLAQEDTPPETDYRLHHVVVYFIQNQAPKKIIEKTLLEQFGDRNLSFDERC 840

Qy        841 HNIMKVAQAKLEMIKPEEVNLEEYEEWHQDYRKFRETTMYLIIGLENFQRESYIDSLLFL 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        841 HNIMKVAQAKLEMIKPEEVNLEEYEEWHQDYRKFRETTMYLIIGLENFQRESYIDSLLFL 900

Qy        901 ICAYQNNKELLSKGLYRGHDEELISHYRRECLLKLNEQAAELFESGEDREVNNGLIIMNE 960
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        901 ICAYQNNKELLSKGLYRGHDEELISHYRRECLLKLNEQAAELFESGEDREVNNGLIIMNE 960

Qy        961 FIVPFLPLLLVDEMEEKDILAVEDMRNRWCSYLGQEMEPHLQEKLTDFLPKLLDCSMEIK 1020
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        961 FIVPFLPLLLVDEMEEKDILAVEDMRNRWCSYLGQEMEPHLQEKLTDFLPKLLDCSMEIK 1020

Qy       1021 SFHEPPKLPSYSTHELCERFARIMLSLSRTPADGR 1055
              |||||||||||||||||||||||||||||||||||
Db       1021 SFHEPPKLPSYSTHELCERFARIMLSLSRTPADGR 1055
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